REMARKS

I. Status of Claims

Upon entry of the present amendment, claims 21, 22, 24, 27, 30, 31, 34-36, 39, 42, 43, and 46-52 will be pending and under examination, claims 23, 25, 26, 28, 29, 32, 33, 37, 38, 40, 41, 44, and 45 having been cancelled herein without prejudice. Claims 21, 27, and 34 are presently amended. No new matter is added by way of the present claim amendments.

II. Rejection Under 35 US.C. § 112, First Paragraph

Claims 23, 28, 29, 40, and 41 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. *See*, Office Action at pages 5-6.

Without in any way acquiescing to the propriety of this rejection, Applicants have cancelled claims 23, 28, 29, 40, and 41. Accordingly, this rejection is moot.

III. Rejection Under 35 U.S.C. § 103(a)

Claims 21-25, 27, 30-32, 34-37, 39, 42-44, and 46-52 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 6,034,235 in view of Hammond et al., *Nature Genetics*, 2:110-119 (2001) and WO 03/061386A1. *See*, Office Action at pages 7-15.

The Office Action alleges that U.S. Patent No. 6,034,235 teaches an antisense molecule that is 100% identical to a 17AA site of a WT1 gene transcript and that the antisense molecule could be used to regulate leukemogenesis. The Office Action further alleges that one of ordinary skill in the art would have arrived at Applicants' claimed siRNA molecule because the ordinary artisan would have been motivated to substitute the antisense molecule of U.S. Patent No. 6,034,235 with an siRNA molecule "since it is obvious to substitute one functional equivalent for another, particularly when they are to be used for the same purpose" and "since Hammond et al. taught that RNA interference is superior to antisense." It is the Office Action's position that the ordinary artisan would have expected success at making the claimed siRNAs because U.S. Patent No. 6,034,235 taught the successful use and design of an antisense molecule targeted to a 17AA site of a WT1 gene transcript

and "KSR forecloses that the simple substitution of one known element for another would have yielded predictable results at the time of the invention." *See*, Office Action at pages 14-15.

According to MPEP § 2143.02, "[a] rationale to support a conclusion that a claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art." The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986). Whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made. *See*, MPEP § 2143.02 (III). Applicants respectfully submit that there was no reasonable expectation that Applicant's claimed invention would be successful, for the reasons discussed below.

There are three independent claims in the present application: claims 21, 27, and 34. Presently amended independent claim 21 is drawn to an siRNA molecule comprising a sense strand hybridized to an antisense strand, wherein the antisense strand targets a region in a 17AA site of a Wilms' tumor gene transcript, the siRNA suppresses cell growth, the sense strand comprises SEQ ID NO: 1, and the antisense strand comprises SEQ ID NO: 2. Presently amended independent claim 24 is directed to a DNA comprising a sequence that is transcribed into a sense RNA strand and an antisense RNA strand that hybridize together to form an siRNA that suppresses cell growth, wherein the antisense RNA strand targets a region in a 17AA site of a Wilms' tumor gene transcript, the sense RNA strand comprises SEQ ID NO: 1, and the antisense RNA strand comprises SEQ ID NO: 2. Finally, currently amended independent claim 34 is directed to a pair of DNAs, the first DNA comprising a sequence that is transcribed into a sense RNA strand and the second DNA comprising a sequence that is transcribed into an antisense RNA strand, wherein the sense and antisense RNA strands hybridize together to form an siRNA that suppresses cell growth, the antisense RNA strand targets a region in a 17 AA site of a Wilms' tumor gene transcript, the sense RNA strand comprises SEQ ID NO: 1, and the antisense RNA strand comprises SEQ ID NO: 2.

U.S. Patent No. 6,034,235 discloses, in relevant part, the exon 5 sequence of WT1 as SEQ ID NO:14 and states that an antisense oligonucleotide derivative to this sequence may be used to suppress levels of WT1 (Applicants' SEQ ID NO:1 is contained within SEQ ID NO:14 of U.S.

Patent No. 6,034,235) (*see*, U.S. Patent No. 6,034,235, col. 2, ll. 21-25; and col. 15). The Office Action appears to assume that, based on this disclosure and the teachings of Hammond, the ordinary artisan would have expected an siRNA molecule that targets U.S. Patent No. 6,034,235's SEQ ID NO:14 to suppress WT1 levels. The Office Action alleges that there is expectation of success because U.S. Patent No. 6,034,235 teaches "the "successful use and design of an antisense molecule targeted to exon 5" (see, Office Action, page 14, last paragraph). Applicants cannot find any disclosure in U.S. Patent No. 6,034,235 of the "successful" (or indeed any) use of such an antisense molecule, and ask the Examiner to identify this alleged disclosure. Insofar as Applicants can ascertain from U.S. Patent No. 6,034,235, it appears that no antisense molecule targeted to exon 5 was ever actually made, much less shown to have any effect. Further, even if U.S. Patent No. 6,034,235 had shown that this hypothetical antisense molecule that targets SEQ ID NO:14 could indeed suppress expression of WT1, nothing in U.S. Patent No. 6,034,235, Hammond and/or WO 03/061386A1 teaches that success with a particular antisense molecule is predictive of success with siRNA that targets the same sequence targeted by the antisense molecule. In fact, the ordinary artisan at the time of the filing of this application was fully aware of the unpredictability of individual siRNAs. For example, Davies et al., *Human Molecular Genetics,* 13:235-246 (2004) (document A8 in the Information Disclosure Statement filed January 18, 2008), state in the context of studies with siRNAs for WT1, "It has been documented that, while siRNA is generally highly effective in repressing gene expression in mammalian cells, **the effectiveness of any particular siRNA is difficult to predict**." (*see*, the carryover sentence of pages 236-237; emphasis supplied). In addition, McManus et al., *J. Immunol.*, 169:5754-5760 (2002) (document 1 in the Information Disclosure Statement filed on September 21, 2010) states, in relevant part, "we observed that the **majority of** the synthetic CD4 and CD8a **siRNAs were noneffective at silencing**. . . An examination of the nucleotide sequences did not reveal any obvious differences between the effective and ineffective siRNAs" (page 5747, left column, first full paragraph; emphasis supplied). McManus shows that only one out of five siRNAs targeting CD4 mRNA was capable of reducing expression of CD4. Both Davies and McManus establish the unpredictability associated with the siRNA field. Based on this unpredictability, and the fact that U.S. Patent No. 6,034,235 did not demonstrate success even with an antisense molecule targeting SEQ ID NO:14, the ordinary artisan at the time of the filing of the present application would not have had any reasonable expectation that an siRNA version of U.S.

Patent No. 6,034,235's hypothetical antisense molecule targeting SEQ ID NO:14 would be able to suppress WT1 expression.

The pending independent claims in this application have been presently amended to require that the siRNA molecule comprises a sense strand comprising SEQ ID NO:1 and an antisense strand comprising SEQ ID NO:2. Applicants have shown that siRNAs that meet these claim limitations were effective in suppressing WT1 mRNA expression (*see*, Example 4, page 14); suppressing WT1 protein expression (*see*, Example 6, page 17); and suppressing growth of HT-1080 fibrosarcoma cells transfected with a vector encoding such siRNAs (*see*, Example 3, page 14 and Example 7, pages 17-18). This could not have been predicted based on the hypothetical musings of U.S. Patent No. 6,034,235 regarding antisense molecules, particularly given the well-known unpredictability of siRNAs in general.

In addition to the remarks above, Applicants also respectfully submit that the art at the time of the filing of this application actually taught away from the claimed invention. These teachings-away were noted in Applicants' prior response filed July 21, 2009, and are repeated here for the Examiner's benefit.

In *KSR Int'l Co. v Teleflex, Inc.*, 550 U.S. 398 (2007), the Supreme Court reaffirmed the principle that "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." The Federal Circuit has described the standard for a *teaching away* as follows: "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference or would be led in a direction divergent from the path that was taken by the applicant." *Optivus Tech., Inc. v. Ion Beam Applications S.A.*, 469 F.3d 978, 989 (Fed. Cir. 2006). Obviousness must be viewed in the context of the art as a whole. *See*, MPEP § 2141.02(I).

As noted by the present specification at page 1, lines 10-14, there are four known splice variants of the WT1 gene. One of the splice variants contains both the 17AA site (in exon 5 of the WT1 gene, according to www.ncbi.nlm.nih.gov/nucleotide/65508003) and the KTS site (in exon 9); one contains neither the 17AA site nor the KTS site, one contains the 17AA site but not the KTS site, and the fourth contains the KTS site but not the 17AA site. Murata et al., *FEBS Letts.*, 409:41-45 (1997) (cited by the Examiner in the Office Action mailed January 22, 2009) explains that the four

splice variants possess different activities attributable to the presence or absence of the 17AA site and the KTS site (*see*, page 41, first column).

Yamagami et al., *Blood*, 87(&):2878-2884 (1996) (cited by the Examiner in the Office Action mailed January 22, 2009) designed their antisense oligomers to target 20 different selected sites in the WT1 coding and noncoding sequences (*see*, Fig. 1 on page 2879). As can be seen in Fig. 1 of Yamagami, all of the targeted sites were outside of exons 5 and 9, so outside of the 17AA and KTS sites. This ensured that every antisense oligomer tested by Yamagami would target sequence common to all four splice variants. Yamagami found that four of these antisense oligomers were effective at inhibiting growth of leukemia cells (*see, e.g.,* Figs. 1 and 2). Yamagami then examined whether the cell growth-inhibiting effect of these oligomers would be reduced by recombinant overexpression of just one of the four WT1 splice variants in the cells. They found that recombinant overexpression of one of the splice variants (the "full-sized WT1 cDNA") only partially overcame the growth-inhibiting effects of each antisense oligomer, and speculated at page 2881, right column, that this inability to completely restore cell growth by overexpression of the WT1 gene might be because each antisense oligomer was targeting all four splice variants, rather than only the one that was recombinantly overexpressed. This suggests that the WT1-dependent growth of the leukemia cells used in the experiments was attributable to the endogenous expression of at least two and perhaps all four of the WT1 splice variants in the cells. It further suggests that, if maximal inhibition of WT1-dependent cell growth is desired, the best antisense strategy would utilize an antisense oligomer that targets all four splice variants, such as any of the antisense oligomers studied by Yamagami. Nothing in Yamagami would suggest any reason to deliberately select an antisense target that would affect at most only two of the four splice variants. In fact, Applicants see nothing in Yamagami that would suggest selecting an antisense sequence other than one of the four Yamagami actually showed to be effective. Given the failure rate of the antisense oligomers tested by Yamagami (only 4 of 20 proved to be capable of significantly inhibiting cell growth), it is not at all predictable that targeting an antisense oligomer to an entirely different region of the gene would be effective. It is even less predictable that targeting that region with an siRNA instead of an antisense oligomer would work. Thus, Yamagami teaches away from the presently claimed siRNA molecules.

Murata also teaches away from selecting the 17AA site in particular for targeting with antisense or siRNA. Murata showed that recombinant expression of one of the WT1 splice variants

containing the 17AA site in leukemia cells inhibited cell growth and induced apoptotic cell death. *See, e.g.*, page 41, right column, end of first paragraph, and Fig. 2. One of ordinary skill would logically conclude that expression of this particular splice variant ($17AA^+$, KTS^-) is likely to be beneficial in controlling cell growth, and that reducing its level of expression by use of antisense or siRNA that targets the 17AA site would be dangerously counterproductive. Recombinant expression of the other $17AA^+$ splice variant ($17AA^+$, KTS^+) had no effect on cell growth in Murata's cells (*see*, Fig. 2), so reducing this splice variant's level of expression would appear to be pointless.

Thus, both Yamagami and Murata supply reasons to avoid targeting the 17AA site of WT1 in particular.

Furthermore, U.S. Patent No. 6,034,235 itself teaches away from Applicants' claimed invention. First, the examples in U.S. Patent No. 6,034,235 focus on targeting regions other than exon 5: i.e., the transcription capping site, capping region, translation start site, and exon 6. Further, according to Figures 1, 6, and 7, antisense molecules that target the transcription capping site (AS1), capping region (AS2), or translation start site (AS3) worked better at inhibiting cell growth than antisense that targets exon 6 (AS4). Thus, one of ordinary skill in the art reading U.S. Patent No. 6,034,235 would be motivated to use antisense molecules that target somewhere in the expression control regions in preference to in a coding region such as exon 5 or 6. This reference, of course, says nothing about using siRNA.

For at least the foregoing reasons, Applicants assert that these references, taken alone or in combination, do not establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103(a).

CONCLUSION

Applicants respectfully submit that all pending claims are in condition for allowance and thus request the timely issuance of a Notice of Allowability.

The Notice of Appeal filed April 22, 2011 reset the final deadline to file a reply (or appeal brief) to November 22, 2011. Applicants petition for a five month extension of time to respond to the outstanding final Office Action. The Five Month Extension of Time fee in the amount of $2,690 and the RCE filing fee in the amount of $930 are being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 14875-0168US1.

Respectfully submitted,

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